PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P3132WO ORD	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/001418	International filing date *(day/month/year)* 31.03.2004	Priority date *(day/month/year)* 02.04.2003
International Patent Classification (IPC) or national classification and IPC G01N33/533, C07D209/56, C07D333/02, C07B61/00, A61K38/25		
Applicant UNIVERSITY OF NOTTINGHAM et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 15 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 39 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.10.2004	29.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Österle, C Telephone No. +49 89 2399-8120

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29.07.2005
Applicant's or agent's file reference: P3132WO ORD	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001418	31.03.2004	02.04.2003

Applicant: UNIVERSITY OF NOTTINGHAM et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001418

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-5, 7, 8, 11, 12, 16-19, 21, 22, 24, 26-50	as originally filed
6, 9, 10, 13-15, 20, 23, 25	received on 11.04.2005 with letter of 06.04.2005

Claims, Numbers

1-46	filed with telefax on 19.07.2005

Drawings, Sheets

1/1	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 9,12, 13, 22, 34, 35, 37-40,42-45
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9,12, 13, 22, 24, 25, 26, 34, 35, 37-40,42-45

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 25 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 9,12, 13, 22, 34, 35, 37-40,42-45 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 24,26

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
   - ☐ complied with.
   - ☐ not complied with for the following reasons:
4. Consequently, this report has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-8, 10, 11, 14-21, 23, 27-33, 36, 41, 46 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8, 10, 11, 14, 16-21, 23, 27-33, 41, 46
	No:	Claims	
Inventive step (IS)	Yes:	Claims	46
	No:	Claims	1-8, 10, 11, 14, 16-21, 23, 27-33, 41
Industrial applicability (IA)	Yes:	Claims	1-8, 10, 11, 14, 16-21, 23, 27-33, 41, 46
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The Applicant filed amended claims of which many do not find support in the application as originally filed. Claims for which support could not be found/was unclear were not subject to examination. The claims concnerned are claims 9, 12, 13, 22, 34, 35, 37, 38, 39, 40, 42, 43, 44, and 45.

2. No search report was drafted for the subject-matter of claims 24 and 26 since they have not been subject to search for the reason that there exists no unity of the subject-matter of these claims and the searched claims (see below under Item "unity").

3. Present claims 1-23, 25 and 27-45 relate to an extremely large number of possible compounds/products/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/products/methods for which the tag moiety TAG is defined as in formula FI1 on p. 20 of the description.

   Consequently, the present WO-ISA relates only to those parts of the claims which have been subject to search.

   New examples filed with the fax of 06.04.2005 of could therefore not be considered in this IPER, sine subject-matter relating to compounds of these examples was not subject to search.

4. The subject-matter of claim 25 is defined such that the linker is of formula V' as defined in claims 13-14 and the linker moiety is as defined in claim 8. In claims 13-14 V'=Y(Tm)L(JtTag)m. Claim 8 defines the moiety JImLJTm. Claim 8 then does not

define a moiety present in claims 13-14.
The subject-matter of claim 25 then is unclear and consequently was not subject to examination.

Re Item IV
Lack of unity of invention

The problem to be solved by the present application can be seen in providing selective fluorescent ligands for binding at desired receptors giving reliable and effective receptor visualization and receptor selectivity with established pharmacology.

Objection regarding lack of unity already raised in the international search report:

The solution suggested to the problem are compounds of formula I or a library of compounds of formula I. The relevant technical feature of the compounds of claim I is the presence of a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter together with a tag moiety.

1) The compounds of formula V are considered intermediates in the process for making the compounds of formula I and therefore are considered to be unitary with the claims relating to the compounds of formula I.

2)Although the compounds of formula IV can be considered intermediates as well, they are not linked by a single inventive concept with the compounds of formula V. There then exists no unity between the compounds of formula V and IV.
The technical problem to be solved by the second invention can be seen in providing compounds which are a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter which can be linked to another moiety via a linker functionality. This problem has been solved in providing compounds of formula IV. The special technical feature is the structure of the compounds of formula IV. It is apparent that the technical features used to solve the two technical problems are different.
Therefore, there's no technical relationship between claims 15, 24 and 26 and the subject-matter of the claims of the first invention.

Consequently, the application lacks unity contrary to the requirement of Rule 13.1 PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: HEITHIER, HELMUT ET AL: "Synthesis and Properties of Fluorescent .beta.-Adrenoceptor Ligands" BIOCHEMISTRY , CODEN: BICHAW; ISSN: 0006-2960, vol. 33, no. 31, 1994, pages 9126-9134, XP002298679

D2: J.C. MCGRATH ET AL: "Viewing adrenoceptors:past, present and future; commentary and a new technique" PHARMACOLOGY COMMUN, vol. 6, no. 1-3, 1995, pages 269-279, XP009037236

1. Novelty (Article 33(2) PCT):

1.1 The subject-matter of amended claim 1 comprises a proviso which excluding the compounds of D1. D1 then is not relevant for the assessment of novelty anymore.

The subject-matter of amended claim 1 furthermore has been limited in that the definition of L=single bond has been deleted. D2 then is not relevant for the assessment of novelty anymore.

Th subject-matter of claim 1 then can be considered novel.

1.2 The subject-matter of amended claim 3 corresponds to the subject-matter of claim 1 wherein additionally the or each Fl is selected from a red, near ir or blue absorbing dye or from BODIPY 630/650 or BODIPY 630/650X.

The subject-matter of claim 2 therefore can be considered novel as well.

1.3 Since independent claims 1 and 2 are novel, the subject-matter of claims 3-11, 14, 18-21 which is dependent thereof is considered novel as well.

1.4 The subject-mater of independent claim 14 relates to a process for preparing a compound of formula I. Since the compounds of formula I are considered novel, the subject-matter of claim 14 can be considered novel as well.

1.5 The subject-matter of claims 16 and 17 relates to a process for selecting a compound of formula I from a library as defined in claims 1-12. Since the compounds of formula I are considered novel, the subject-matter of claims 16 and 17 can be considered novel as well.

1.6 The subject-matter of claim 23 relates to a kit comprising the compound of formula I or I' as defined in claims 1-12. Since the compounds of formula I are considered novel, the subject-matter of claim 23 can be considered novel as well.

1.7 A claim relating to a library *for use* in a specific application is considered as claim directed to a library *suitable for use* in such an application.

The subject-matter of claims 27-31 then in fact are library claims comprising compounds of formula I as claimed in claims 1 and 2 and can be considered novel.

1.8 The subject-matter o claims 32, 33 and 36 relates to a kit comprising a library or compound of formula I or I' and, since these are considered, is novel as well.

1.9 The subject-matter of claims 41 and 46 relates to compounds falling within the scope of claims 1 and 2. Since the subject-matter of claims 1 and 2 is considered novel, the subject-matter of claims 41 and 46 can be considered novel as well.

2. Inventive Step (Article 33(3) PCT):

2.1 The subject-matter of claim 46 comprises tagged ligands. The ligands differ from the ligands of the state of the art D1 and D2 in that the tags have different chemical structures.

The tags of claim 46 are BODIPY 630/650 which fluoresce red (maximum at ~650

nm), whereas the fluorescent tags of the prior art all fluoresce in the green and orange range (BODIPY FL at ~510 nm; erythrosine at ~550 nm).
This difference has the effect that the compounds of the present invention are more suitable for ligand binding studies since the range of fluorescence of the tags is sufficiently remote from that of the GFP cell stain conventionally used in binding studies (fluoresces in the blue region).

The prior art did not address this problem, therefore the solution suggested in claim 46 is considered non-obvious for the skilled person.

2.2 The subject-matter of claims 1 and 2 relates to libraries of compounds of the formula I.

In view of D1 and D2 the technical problem can be seen in providing a multitude of compounds which visualize GPCR receptor binding (see also discussion of inventive step under 2.1 above).

The nearly infinite possibilities claimed in the library of claims 1 and 2 comprises compounds which will not have the desired properties. A library of compounds can however only be inventive if all compounds solve the (same) technical problem. The presently claimed compounds however cannot be considered to all solve the technical problem since for example in claim 1 the tag can fluoresce in any range of the spectrum. Such compounds would be considered mere alternatives of the tags used in the prior art and cannot be considered inventive.

In view of the disclosure of the description the only part of claim 1 which could be considered inventive is the compounds of formula I for which Tag is a fluorescent red, near ir or blue absorbing dye **and** for which Lig is a GPCR ligand. It is at present not obvious from the description whether compounds for which Tag fulfils the above criteria but for which Lig is an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter solve a technical problem.

The subject-matter of claim 1 therefore does not meet the criteria of Article 33(3) PCT.

In claim 2 **some of the tags** of the compounds of the library are fluorescent red, near ir or blue absorbing dyes. Since however not all compounds falling within formula I are considered to solve the technical problem, the subject-matter of claim 2 also is not considered inventive.

2.3 The subject-matter of dependent claims 3-8, 10, 11, 18-21, 27-31, 36, and 41 does not comprise further technical features which are considered to impart inventiveness on all compounds falling within formula I.

2.4 The process of claim 14 is considered to be analogous to the process disclosed in D1 and therefore cannot be considered inventive.

2.5 The process of claims 16 and 17 comprises methods which are part of the general methodology used in combinatorial library design. In lack of a special technical feature linked to the compounds prepared such general claims cannot be considered inventive.

2.6 The subject-matter of claims 23, 32 and 33 relates to kits of a compound or a library of compounds of formula I. Since not all compounds of said library are considered inventive, a kit comprising these compounds, in lack of an additional inventive technical feature cannot be considered inventive.

2.7 The subject-matter of claim 24 relates to linker moieties which are part of the compounds of formula I. Since not all compounds of said library are considered inventive, such linkers, in lack of an additional inventive technical feature cannot be considered inventive.

Re Item VI

Certain documents cited

S.J. BRIDDON ET AL: "Application of fluorescence correlation spectroscopy to the measurement of agonist binding to a G-protein coupled receptor at the single cell level" FARADAY DISCUSSIONS, vol. 126, 12 September 2003 (2003-09-12), pages 197-207,

XP002298675

J.G. BAKER ET AL: "Pharmacology and direct visualization of BODIPY-TMR-CGP: A long-acting fluorescent beta2-adrenoceptor agonist" BRITISH JOURNAL OF PHARMACOLOGY, vol. 139, no. 2, May 2003 (2003-05), pages 232-242, XP002298676

S.J. BRIDDON ET AL: "Quantitative analysis of the formation and diffusion of A1-adenosine receptor-antagonist complexes in single living cells" PNAS, vol. 101, no. 13, 16 March 2004 (2004-03-16), pages 4673-4678, XP002298677

Re Item VII

Certain defects in the international application

1. Article 34(2)b) PCT:

1.1 The subject-matter of claims 12 and 22 is a mixture of different parts of the description and of specific examples. The combination of definitions now claimed in claims 12 and 22 however is nowhere disclosed in the description.

1.2 No basis could be found for the amended sentence in claim 13 "wherein linking.....defined".

1.3 In claim 9, in the definition of $R.c^2$ a moiety has been added which was not present in the application as originally filed, e.g. the substituent "$C(CH_3)_2CH_2$**Ph**.

1.4 Claim 34 does not find basis on p. 4 of the application since there is disclosed a plurality of defined and characterized *tagged* ligands.

1.5 Claim 35 claims that the library design is the result of extensive *pharmacological* investigation. No support for the expression "pharmacological" could be found.

1.6 The specific combination of definitions in claim 38 no not find support in the description as originally filed.

1.7 The subject-matter of claims 37 and 42 defines $LigJ_LLJ_T$ as being selected from Lig.a, Lig.b, Lig.c, and Lig.d. On pages 10 and following, Lig.a, Lig.b, Lig.c, and Lig.d in contrast represent a moiety Lig.
Furthermore, in the description Lig.a, Lig.b, Lig.c, and Lig.d do not comprise a functionality J_L.

The definition of Ra4 as claimed in claims 37 and 42 also cannot be found in the description.

The substituent Rd1 of claims 37 and 42 comprises wrong structures, which do not find support in the description. Also, a C1-20 spiro aromatic ring system is nowhere disclosed in the description.

1.8 The last formula of claim 38 does not find support in the description.

1.9 Claim 39 is dependent on claim 38. Since this claim is considered not to fulfil the requirements of Article 34(2)b) PCT, the objection under this Article also applies to the subject-matter of claim 39.

1.10 Since claims 37 and 38 are not supported by the application as originally filed, the subject-matter of claim 40, which is dependent thereof, also does not find support.

1.11 The last formula of claim 43 is not supported by the application as originally filed.

1.12 No support could be found for the specific combinations claimed in claim 43.

1.13 Since claims 42 and 43 are not supported by the application as originally filed, the subject-matter of claims 44 and 45, which is dependent thereof, also does not find support.

2. Further objections:

2.1 The new set of claims comprises an unduly large number of independent claims of

the same category which in fact in many cases are claims which comprise subject-matter which could be drafted as dependent claims (Rule 6.1(a)).

2.2 Claims of the same category are not grouped together.

Re Item VIII

Certain observations on the international application

1. **Clarity (Article 6 PCT):**

1.1 Claims 27-31 relate to compounds/libraries and to kits, e.g. two different subject-matters.

1.2 Claim 34 relates to a library comprising a plurality of *defined and characterized ligands having verified properties corresponding to those of the non-tagged ligand.* It is unclear what the expressions "defined", "characterized" and "verified" relate to, e.g. defined *how*, characterized *how* and verified *in which way.*

1.3 The library of claim 35 is defined by a process for preparing the tagged ligands comprised in said library. The process for production of the ligands is however not considered for the assessment of novelty and inventive step of the claim.

1.4 The subject-matter of claim 37 comprises Rd1 which is defined as a C1-20 spiro aromatic ring system. The claim lacks clarity since there is no C1 spiro aromatic ring system.

1.5 The subject-matter of claims 41 and 46 lacks a reference: The sentence "...compound selected from *the structures* wherein...) dos not make sense.

1.6 The third and fourth compounds of claim 41 are identical.

1.7 The expression "with the proviso that the compound is not a compound excluded in claim 18" of claim 42 is unclear since claim 18 does not exclude a specific compound.

1.8 In present claim 1 a library of ligands of formula I is claimed. The expression "library" is unclear since both, an array of compounds, e.g. a collection of individual compounds, and a mixture of compounds fall under this expression.
Present claim 1 therefore lacks clarity (Article 6 PCT).

The same applies mutatis mutandis to all other claims relating to libraries.

Since the exact nature of the library of the claims is not clear, the widest definition comprising an array or mixture is applied for the assessment of novelty and inventive step.

1.9 The sentence "...and *a) -e)* when L is a single bond, Fl is not BODIPY FL.." in claim 21 does not make sense and is not supported by the application as originally filed.

1.10 The library of claim 30 is defined by a functional parameter relating to the detection process used to detect these compounds. Such a parameter is not suitable to define the compounds of the library and is not seen as limiting to the subject-matter of claim 30.

More preferably a library comprises a plurality of compounds of one or more of formula II to III'':

II $(LigJ_L)_m$ L J_T TagJ_T L $(J_L$ Lig$)_m$ where each m is as hereinbefore defined and is preferably 1 or 2, more preferably 1

III $(LigJ_L)_m$ L $(J_T$Tag$)_m$ wherein each m is as hereinbefore defined and is preferably 1 and/or 2, more preferably

Lig J_L – L – J_L Tag and/or

Lig J_L – L – J_T Tag and/or Lig J_L – L – J_T Tag
$\backslash J_L$ Lig $\backslash J_T$ Tag

wherein each J_L and J_T comprises J as hereinbefore defined and may be same or different and may derive from functionality originally present in Lig or L and Tag or L or a combination thereof, characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L, L, J_T and/or Tag, and is at different linking sites in the case of any two or more compounds comprising identical Lig, J_L, L, J_T and/or Tag.

In one preferred embodiment the invention comprises a library of compounds of formula I as hereinbefore defined wherein Lig, J_L, L, J_T and Tag are the same in all compounds, and wherein the compounds differ by site of linking thereof.

In a further preferred embodiment the invention comprises a library of compounds of formula I or I' as hereinbefore defined wherein Lig and J_L are the same in all compounds and L and J_T are the same or similar in all compounds and Tag is different in some or all compounds.

In a further preferred embodiment the invention comprises a library of compounds of formula I or I' as hereinbefore defined wherein Lig- and –Tag are the same in all compounds and –L- is different in all compounds.

The library may comprise from 3 to 250 tagged ligands. Preferably the library comprises from 1 to 10 families comprising 3 to 25 tagged ligands each family comprising a ligand moiety of a common ligand type and from 3 to 25 different tag moiety types at least one of which is a fluorescent tag, more preferably each of which is a different fluorescent tag; or the library comprises from 5 to 250 fluorescently tagged ligands of different ligand type and different fluorophore type.

A library providing fluorescent ligands comprising different Fl is useful to enable studying binding, inhibition or transport with different colour fluorescence for example to distinguish from same colour native fluorescence or to distinguish plural types of binding site, enzyme, transporter or the like.

It is known that ligands modified ie by linking to a fluorophore typically undergo a change in binding affinity, inhibition or transport and suitably the library of the invention comprises characterisation of the pharmacology of each compound including binding affinity or inhibition or transport for certain GPCRs, intracellular enzymes or drug transporters. Preferably the library includes information for each

In the case that L comprises a single or double bond, J_L and J_T if present may comprise functionality derived from a reactive group or site for linking linker and fluorophore derived from the fluorescent moiety and/or the ligand moiety.

Preferably the moiety J_{Lm} L J_{Tm} comprises a mono, di, tri, tetra, penta or hexa amino, alkylthio, alkoxy, carboxylic acid, and combinations thereof more preferably a mono, di or tri aminoalkylthio, amino alkoxy, alkoxy carboxylic acid, alkoxy amine and the like. Preferably J_{Lm} L J_{Tm} is selected from mono, di or tri amino menthane, amino ethane, thio ethane, ethane, amino acyl, from polypeptide, or from mono or polyether derivatives thereof eg diamine or dithio such as mono or polyethylene glycol di or tri amine or thio.

Preferably a linker moiety J_{Lm} L J_{Tm} as hereinbefore defined comprises a single or double bond or a single atom or group as hereinbefore defined or comprises a mono-, di-, tri- or tetrafunctional linear or branched or cyclic substituted or unsubstituted hydrocarbyl of formula –L.I-

$$J.[\,A\,]\,q_L\,R_L\,[\,A'q_{L'}\,J'\,]_p\,A''q_{L''}\,J''$$

wherein each of J to J'' is a linking site or functionality as hereinbefore defined independently selected from a single bond, methylene, alkyne, alkene, NR, O, NRCO, S, CO, NCO, CHHal, P and the like wherein R is H or C_{1-8} alkyl or cycloalkyl or forms part of a cyclic ring with N, Hal is any halogen selected from chlorine, iodine, bromine; and is present in any rational location in a group A to A'';

each of A to A '' is a group selected from –O-, -C(=O)-, C_{1-12} alkoxy, alkoyl, cycloalkyl, heterocyclic, alkyl, alkenyl, aryl, arylamide, arylamine, amino, thioalkyl, heteroaryl as hereinbefore defined and combinations thereof and the like, optionally substituted by groups selected independently from C_{1-3} alkyl, C_{1-5} alkoxy and the like;

each of q_L to q_L'' are independently-selected from 0 or 1 or indicates an oligomeric repeat and is from 2 to 30, or indicates a polymeric repeat unit and is from 31 up to 300.

R_L is a C, N or S atom or is a $CR_{L'}$, $NR_{L'}$, alkyl, cycloalkyl, heterocyclic, aryl heteroaryl, amine or thio moiety and provides for branching when p is 1 or 2; wherein $R_{L'}$ is H or C_{1-3} alkyl; and

p is as hereinbefore defined and is 0, 1 or 2.

Preferably each J, J' and J'' independently is a single or double bond, NR_L, -O or –S or –C(O) or -NRC(O) or -C(O)NR, as hereinbefore defined

A is alkoxy preferably CH_2CH_2O (PEG) and oligomers thereof or is aralkylamine aralkylamide, aralkyloxy, or is alkyl, preferably $(CH_2)_{1-12}$

R_L is a C_{1-5} alkyl chain comprising or containing a single or double branching C atom when p is 1 or 2;

p is 0, 1 or 2;

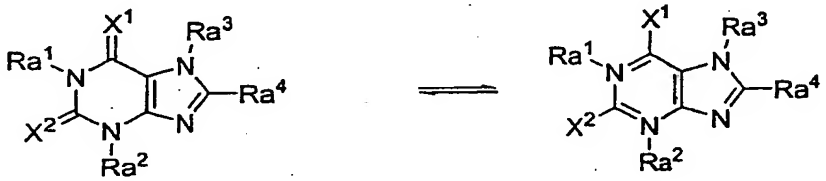
A' and A'' are each selected from C_{1-8} alkyl, amine, phenylamine, phenylamide; and

q_L is 0, 1, 2 to 30 or 31 to 300, and $q_{L'}$ and $q_{L''}$ are 0 or 1

More preferably J_{Lm} L J_{Tm} is a single bond or is of formula
J Aq_L R_L J''
wherein each of J and J'' is amine or –O-, A is CH_2CH_2O, q_L is 1-30 or 31 to 300 and R_L is CH_2CH_2
or of formula
J Aq_L R_L(A'J') J''
wherein each of J, J' and J'' independently is amine, –O or a single bond, q_L is 1, 2 or 3 -30 or 31 to 300 and A is CH_2CH_2O or $HNCH_2CO$ or q_L is 1 and A is C(O) or $(CH_2)_{1-8}$ or q_L is 0, R_L is CH or CH_2CH, q_L' is 0 or q_L' is 1 and A' is CH_2 and q_L'' is 0
preferably
$O(CH_2CH_2O)q_LCH_2CH_2NH$, $O(CH_2CH_2O)q_LCH_2CH(CH_2NH)NH$,
$OCH(CH_2NH)NH$, -$CH(CH_2NH)NH$, -C(O) NH-, -$(CH_2)_{1-8}$-, (-$HNCH_2CO$-)$_{1-3}$ (= -gly_{1-3}-) - or the like.

More preferably each compound of formula I or I' as hereinbefore defined comprises a moiety Lig and L as hereinbelow defined:
Wherein:
Lig.a_m is suitably of the formula, in either of the following forms given, including any of its possible linking configurations or sites:

Lig.$a^1{}_m$

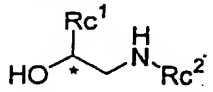


Wherein any or each of Ra^1 to Ra^4, X^1 and X^2 may comprise a linking site or functionality J as hereinbefore defined
X^1 and X^2 are each independently selected from H, O, OR.a, NR.a, NHR.a;
X^1 and X^2 are each preferably O;
each of $R.a^1$, $R.a^2$, $R.a^3$ and $R.a^4$ independently is selected from H or C_{1-4} linear or branched alkyl, preferably H, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl or isobutyl optionally mono or multi hydroxy or halo substituted, such as CH_2OH, CH_2F or $CH_2CHOHCH_2OH$;
$R.a^4$ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore

is as hereinbefore defined for L or its subformulae, more preferably is saturated and unsaturated substituted or unsubstituted C_{1-12} aliphatic or C_{1-24} aromatic as defined for L preferably including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, more preferably is of formula L.I or its subformulae as hereinbefore defined, most preferably is (CH_2)m wherein m is 2 to 12, preferably 3, 4, 6 or 8, or is (Ph-$CH_2CONH)_2$ $(CH_2)_2$;

Lig.c is suitably of the formula Lig.c including any of its possible linking configurations or sites:

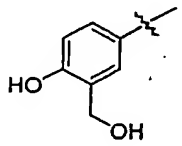
Lig.c $HOC^*(R.c^1)CH_2NH\text{-}R.c^2$



Where any or each of Rc^1 to Rc^2 or OH, or a chain C or N may comprise a linking site or functionality J as hereinbefore defined

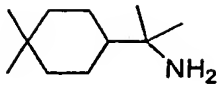
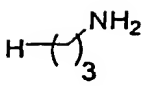
* indicates an optically active centre and

Wherein $R.c^1$ is C_{6-14} aryl optionally including one or more heteroatoms selected from H, O, optionally substituted by OH, Hal eg Cl, NH_2, NHC_{1-3}alkyl, sulphonamide, oxoamine (-$CONH_2$) and the like, more preferably mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH_2, more preferably m-CH_2OH, p-OH phenyl, m-,p-dihydroxy phenyl or m-,m-dihydroxyphenyl, m-,m-diCl, p-NH_2 phenyl, p-OH, m-$CONH_2$ phenyl or 5-OH, 8-quinoline and the like, such as



$R.c^2$ is selected from saturated or unsaturated, substituted or unsubstituted C_{1-20}, preferably C_{1-12}, branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any optionally substituted C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like and combinations thereof;

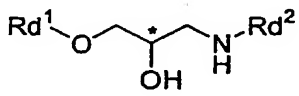
Preferably $R.c^2$ is selected from C_{1-6} branched or straight chain aliphatic, C_{6-10} araliphatic optionally substituted by OH and optionally including heteroatoms selected from N,O, preferably including an ether O, such as selected from $-(CH_2)_6OCH((CH_2)_3Ph)$, $CHCH_3(CH_2)_2Ph$, $CHCH_3CH_2PhOH$, $C(CH_3)_2CH_2Ph$ or from the structures:

L.c may be present as $R.c^2$ or may comprise a linking site or functionality J as hereinbefore defined, and is as hereinbefore defined for L and is suitably of formula L.I or its subformulae as hereinbefore defined, more preferably is selected from C_{1-12} alkyl, amide etc;

Lig.d is suitably a non-peptide of the formula Lig.d including any of its possible linking configurations or sites:

Lig.d $R.d^1\ OCH_2C^*HOHCH_2NH\text{-}R.d^2$

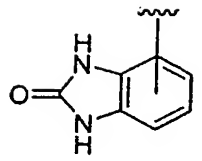
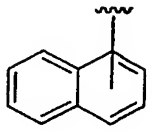
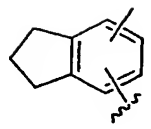
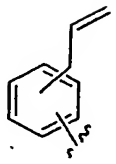
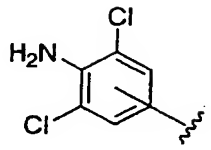


where any or each of Rd^1 to Rd^2 or OH, a chain C or N may comprise a linking site or functionality J as hereinbefore defined

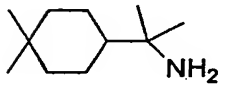
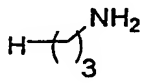
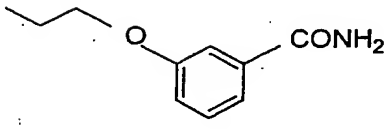
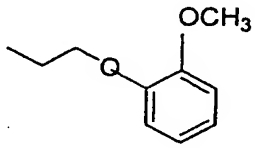
* indicates an optically active centre

Wherein $R.d^1$ is saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

Preferably $R.d^1$ is substituted or unsubstituted C_{1-24} aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C_{1-6} alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo such as chloro or OH, preferably $R.d^1$ is unsubstituted or substituted alkyl, alkenyl, halo, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, illustrated as follows, most preferably mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl such as phenyl, carbazole or structures shown below or spiro ring systems, most preferably mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF_3 substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems most preferably of the structures:

$R.d^2$ is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C_{1-12} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, more preferably amine, C_{1-6} branched or straight chain alkyl optionally including ether O, and optionally substituted by C_{6-10} aryl, for example i.pr, i.bu, or of the formula:

L.d may be present as $R.d^2$ or may comprise a linking site or functionality J as hereinbefore defined and is as hereinbefore defined for L and its subformulae and is suitably of formula L.I and its subformulae as hereinbefore defined, more preferably is a single bond or is as hereinbefore defined for L.a;

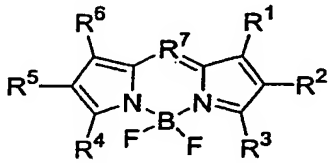
Lig.e comprises a cell permeant moiety or is associated with a cell permeant L or Fl moiety and is suitably of the formula , in either of the following forms given including any of its possible linking configurations or sites:

derived from linking via a reactive group as hereinbefore defined such as carboxyl, sulphonate or as a heteroatom such as O or S or methylene derived from linking at an alkylhalide such as methylbromide, haloacetamide, sulphonate ester or the like electrophilic group.

Fl may include a substituent –t- as hereinbefore defined which is heteroaryl or alkenyl such as mono-, di- or tri -enyl group which shifts the fluorescence of the compound to the red part of the spectrum and raises the absorption max value as in US 5187288; or may include alkenyl substituent linked to one or more of an aryl, carbonyl or like group, preferably linked to a fatty acid sidechain comprising $(CH_2)nCO_2H$ where n = 5 – 22 as in US 5330854, more preferably linked via an aryloxymethylene to a and carbonyl; or may include an aryl alkenyl aryl group as in US 6005113.

More preferably -Fl is of the formula -Fl^1:

Fl^1 dipyrrometheneborondifluoride analogues including any of its possible linking configurations or sites:

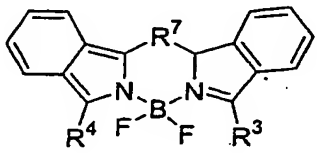


Wherein any or each of R^1 to R^7, or a ring atom may comprise a linking site or functionality J as hereinbefore defined

R7 is N or C-R8;

Substituents R^1, R^2, R^3, R^4, R^5, R^6 and R^8 which may be the same or different are H, halogen, nitro, sulfo, cyano, alkyl, perfluoroalkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, arylalkyl, or acyl wherein the alkyl portions of each contain fewer than 20 carbons; or substituted or unsubstituted aryl or heteroaryl; preferably at least four of R^1 to R^8 are non-hydrogen, alternatively adjacent substituents R1 and R2 taken in combination and adjacent substituents R5 and R6 taken in combination form fused 6-membered (hetero) aromatic rings

or



including any of its possible linking configurations or sites:

wherein any or each of R^3, R^4 or R^7, or a ring atom may comprise a linking site or functionality J as hereinbefore defined

each fused ring is optionally and independently substituted by H, halogen, nitro, sulfo, cyano, alkyl, perfluoroalkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, alkylthio, alkylamido, amino, (mono or dialkyl)amino (wherein the alkyl portions of each

linker precursors wherein linking may be at same or different reactive sites in different compounds as hereinbefore defined.

Preferably the process is a combinatorial process. Preferably the process comprises the reaction of one or more ligand precursors of formula IV and/or IV'

IV $(LigJ_L)_m-L-Y_{Ln}$

IV' $Lig\ Y_{Lign}$

comprising one or more or different reactive groups Y_L or Y_{Lig} forming a linking functionality J, J_L or J_T as hereinbefore defined

with one or more of a plurality of analytical tagging substrates of formula V and/or V'

V $Y_{Tm}\ Tag$

V' $Y_{Tm}\ L\ (J_T Tag)_m$

comprising one or more or different reactive groups Y_T forming a linking functionality J or J_T as hereinbefore defined

and optionally one or more linking species VI or VI' or VI''

VI $Y_{Lm}\ L\ Y_{Lm}$

wherein Lig, J, L, J_T and Tag and each m is independently as hereinbefore defined wherein the or each compound of formula IV or IV' is capable of reaction with the or each compound of formula V or V', optionally via the or each species VI or VI' or VI'' to form a plurality of compounds of formula I as hereinbefore defined.

Preferably in some or each compound of formula V or V', Tag is Fl as hereinbefore defined, whereby the process is a process for preparing a library comprising a plurality of compounds of which one or more or all of which are of formula I' as hereinbefore defined.

Suitably reactive groups Y_{Lig}, Y_L, Y_T have suitable reactive group functionalities for linking, as hereinbefore defined, for example by substitution or by addition or addition – elimination reaction. Substitution reaction is suitably selected from reaction of electrophilic and nucleophilic reactive sites as hereinbefore defined such as:

Electrophilic Y	Nucleophilic Y	Resulting covalent Linkage, J	leaving groups
Carboxylic acid	alcohol	ester	-OH, -H
Carboxylic acid	amine	carboxamide	-OH, -H
Carboxylic acid	hydrazine	hydrazide	-OH, -H
Alkyl halide	alcohol	ether	-Hal, -H
Alkyl halide	thiol	thioether	-Hal, -H
Alkyl halide	amine	alkylamine	-Hal, -H
Alkyl halide	COOH	ester	-Hal, -H
Haloacetamides	thiols	thioethers	-Hal, -H
Sulphonate esters	amines	alkyl amines	RSO_3-, -H
Sulphonate esters	alcohols	ethers	RSO_3-, -H
Sulphonate esters	thiols	thioethers	RSO_3-, -H
Sulphonyl halides	amines	sulphonamides-Hal,	-H
Sulphonyl halides	alcohols	sulphonate esters	-Hal, -H

known methods which prejudice yields by use of non chemoselective reactive groups or protecting groups.

Preferably the compounds of formula I or I' are obtained by:
reacting the unprotected primary alkyl amine group of a compound of formula IV as hereinbefore defined with a compound of formula V comprising a reactive succinimidyl ester group in solvent at ambient temperature without need for subsequent deprotection. In a particular advantage of the invention the method provides greater yield than with the prior art processes.

Compounds of formula IV, IV', V', V' or VI may be commercially available or may be prepared by known means. A linker may be installed as an independent entity or may be constructed as part of a synthetic process as hereinbefore defined, preferably is synthesised as an additional substituent on the ligand moiety or fluorescent moiety prior to reaction thereof.

In a further aspect of the invention there is provided a process for the preparation of a compound of formula I as hereinbefore defined comprising the reaction of a compound of formula IV or IV' and a compound of formula V or V' and optionally additionally VI, as hereinbefore defined.

In a further aspect of the invention there is provided a process for the preparation of a compound of formula IV as hereinbefore defined comprising: obtaining where commercially available or preparing the ligand precursor Lig, by routes as known in the art, and reacting with linker precursor VI'', if required, or components thereof, and/or generating one or more reactive sites Y or Y_{Lig} or Y_L. Protection of IV may be required in which case reaction is followed by removing any protecting group present during the reaction, optionally replacing with a protecting group which may be removed under ambient conditions. A reactive group Y or Y_{Lig} or Y_L is preferably selected from groups as hereinbefore defined.

Preferably the process comprises:
a), e) ring closure of 5,6-diamino-1,3-dialkyl uracil with the appropriate substituted aldehyde under acid conditions with ferric chloride,
b) reacting Lig.b- comprising a protected inosine derivative with chlorinating agent and linking the chloro derivative with the amine group of a suitably protected amine reactive linker H–L-P_L wherein P_L comprises *N*-benzyloxycarbonyl- to form Lig.b - L-P_L and removing P_L to generate Lig.b –L.b; preferably $R.b^1$ comprises a OH terminating group and protected inosine comprises Acyl protecting groups or $R.b^1$ comprises a stable group such as amine or amide and protected inosine comprises 2,2-dimethoxypropane protecting group; preferably the protected inosine is reacted with oxidising agent and protected alkylamine which is an *N*-alkylcarboxamide with removal of amine protecting group to generate a reactive ligand;
c), d) reacting *p*-hydroxybenzaldehyde with formaldehyde under acid catalysis and protection of the resulting 4-hydroxy-3-hydroxymethylbenzaldehyde with dimethoxypropane to generate the resulting acetonide. Converting the Benzaldehyde to its corresponding epoxide and ring opening with a suitably protected linker such as

CLAIMS

1. Library comprising a plurality of tagged ligands of formula I

$$(Lig\ J_L)_m\ L\ (J_T\ Tag)_m\ (J_T\ L\ (J_L\ Lig)_m)_p$$

and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers
comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_T and J_L
wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is selected from a double bond, -O-, -S-, amine, COO-, amide, -NN- hydrazine; and saturated or unsaturated, substituted or unsubstituted $C_{1\text{-}600}$ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any $C_{1\text{-}20}$ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;

Tag is any tagging substrate;

m are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which are of formula I'

$(LigJ_L)_m\ L\ (J_T\ Fl)_m\ (J_T\ L\ (J_LLig)_m)_p$

characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L, L J_T and/or – Tag and is at different linking sites in compounds comprising same Lig, J_L, L J_T and/or – Tag
with the proviso that when Lig is CGP12177 and L is 1,1,4,4-tetramethyl butylamine $C(CH_3)_2(CH_2)_2C(CH_3)_2NH$-, Fl is not BODIPY® FL, or when L is $C(CH_3)_2(CH_2)_2$-$C(CH_3)_2NHCSNH$ – then Fl is not FITC, eosin or erythrosin.

2. Library comprising a plurality of tagged ligands of formula I

$$(Lig\ J_L)_m\ L\ (J_T\ Tag)_m\ (J_T\ L\ (J_L\ Lig)_m)_p$$

and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers
comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_T and J_L

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wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is selected from a double bond, -O-, -S-, amine, COO-, amide, -NN- hydrazine; and saturated or unsaturated, substituted or unsubstituted C_{1-600} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C_{1-20} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;

Tag is any tagging substrate;

m are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which are of formula I'

$(LigJ_L)_m\ L\ (J_T\ Fl)_m\ (J_T\ L\ (J_L Lig)_m)_p$

wherein linking is at same or different linking sites in compounds comprising different Lig, J_L, L J_T and/or – Tag and is at different linking sites in compounds comprising same Lig, J_L, L J_T and/or – Tag

with the proviso that when Lig is CGP12177 and L is 1,1,4,4-tetramethyl butylamine $C(CH_3)_2(CH_2)_2C(CH_3)_2NH$-, Fl is not BODIPY® FL, or when L is $C(CH_3)_2(CH_2)_2$-$C(CH_3)_2NHCSNH$ – then Fl is not FITC, eosin or erythrosin

characterised in that the or each Fl is selected from a red, near ir or blue absorbing dye or from BODIPY® 630/650 or BODIPY® 630/650 X.

3 Library as claimed in any of Claims 1 to 2 wherein each compound of formula I or I' comprises one of a plurality of fluorophores and/or tags providing a library of differently fluorescently tagged ligands comprising one or a number of different fluorophores optionally of different chemical composition or spectral characteristics; and/or providing a library of differently tagged ligands including at least one fluorescently tagged ligand; alternatively each compound of formula I or I' comprises one of a plurality of precursor ligands linked each to one or a plurality of different tags providing a library of same or differently tagged ligands of plural ligand type; alternatively each compound of formula I comprises one of a plurality of linkers linking a precursor ligand and at least one Tag at the same or different linking site; alternatively each compound of formula I comprises the same linker linking a precursor ligand and at least one Tag at different linking sites providing a library of differently linked tagged ligands of different conformation or anticipated pharmacology and binding.

4 Library as claimed in any of Claims 1 to 3 comprising a plurality of compounds of one or more of formula II to III:

II $(LigJ_L)_m\ L\ J_T\ TagJ_T\ L\ (J_L\ Lig)_m$ where each m is as hereinbefore defined and is preferably 1 or 2, more preferably 1

III $(LigJ_L)_m$ L $(J_TTag)_m$ wherein each m is as hereinbefore defined and is preferably 1 and/or 2, more preferably
Lig J_L – L – J_L Tag and/or
Lig J_L – L – J_T Tag and/or Lig J_L – L – J_T Tag
$\searrow J_L$ Lig $\searrow J_T$ Tag

wherein each J_L and J_T comprises J as hereinbefore defined and may be same or different and may derive from functionality originally present in Lig or L and Tag or L or a combination thereof, characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L, L, J_T and/or Tag, and is at different linking sites in the case of any two or more compounds comprising identical Lig, J_L, L, J_T and/or Tag.

5 Library as claimed in any of Claims 1 to 4 including information for each compound of formula I comprised in the Library, relating to the pharmacology for binding to or inhibition of a GPCR receptor or to inhibition of an intracellular cyclic nucleotide phosphodiesterase, or inhibition of or transport by a drug transporter including designation as agonist, antagonist, substrate or inhibitor and measure of affinity or inhibition, enabling quantification of results.

6 Library as claimed in any of Claims 1 to 5 wherein a GPCR ligand is selected from any compound which is effective as an agonist or antagonist for an adenosine receptor, a beta-adrenoceptor, a muscarinic receptor, a histamine receptor, an opiate receptor, a cannabinoid receptor, a chemokine receptor, an alpha-adrenoceptor, a GABA receptor, a prostanoid receptor, a 5-HT (serotonin) receptor, an excitatory aminoacid receptor (glutamate), a dopamine receptor, a protease-activating receptor, a neurokinin receptor, an angiotensin receptor, an oxytocin receptor, a leukotriene receptor, a nucleotide receptor (purines and pyrimidines), a calcium-sensing receptor, a thyroid-stimulating hormone receptor, a neurotensin receptor, a vasopressin receptor, an olfactory receptor, a nucleobase receptor (adenosine), a lysophosphatidic acid receptor, a sphingolipid receptor, a tyramine receptor (trace amines), a free-fatty acid receptor and a cyclic nucleotide receptor; an inhibitor of intracellular enzymes is an inhibitor of cyclic nucleotide phosphodiesterases; and a substrate or inhibitor of a drug transporter is selected from a substrate or inhibitor of an equilibrium based drug transporter or ATP driven pump selected from a catecholamine transporter, a nucleoside transporter, an ATP-binding cassette transporter, a cyclic nucleotide transporter or derivatives or analogues thereof ;
or wherein Lig is selected from
a) xanthine like structures including XAC, theophylline, caffeine, theobromine, dyphilline, enprofylline; or fused biaryl structures including papaverine, dihydroquinilones, cilostamide, dipyridamole or vinpocetine; and analogues thereof;
b) adenosine like structures including ADAC, NECA and analogues thereof;
c) ethanolamine like structures including salmeterol, salbutamol, terbutaline, quinprenaline, labetalol, sotalol, bambuterol, fenoterol, reprotolol, tulobuterol, clenbuterol and analogues thereof;
d) oxypropanolamine like structures including CGP12177, propranolol, practolol, acebutalol, betaxolol, ICI 118551, alprenolol, celiprolol (celectol), metoprolol (betaloc), CGP20712A, atenolol, bisoprolol, misaprolol, carvedilol, bucindolol, esmolol, nadolol, nebivolol, oxprenolol, xamoterol, pindolol, timolol and analogues thereof;

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e) xanthine like structures including XAC, theophylline, caffeine, theobromine, dyphilline, enprofylline, sildenafil, EHNA (erythro-9-(2-hydroxyl-3-nonyl)adenine), zaprinast; or spiro bicyclic structures including bypyridines, amrinone; imidazolines, CI930; dihydropyridazinones, indolan, rolipram, SB207499; or fused biaryl structures including papaverine, dihydroquinilones, cilostamide, dipyridamole, vinpocetine and analogues thereof.

7 Library as claimed in any of Claims 1 to 6 wherein J_{Lm} L J_{Tm} comprises a mono, di, tri, tetra, penta, or hexa amino, alkylthio, alkoxy, carboxylic acid, and combinations thereof including a mono, di or tri aminoalkylthio, amino alkoxy, alkoxy carboxylic acid or alkoxy amine, mono, di or tri amino menthane, amino ethane, thio ethane, ethane, amino acyl, polypeptide, or mono or polyether derivatives including diamine or dithio derivatives, mono or polyethylene glycol di or tri amine or thio;
or comprises a mono-, di-, tri- or tetra, penta or hexafunctional linear or branched or cyclic substituted or unsubstituted hydrocarbyl of formula –L.I-

$$J[\,A\,]\,q_L\,R_L\,[\,A'q_{L'}\,J'\,]_p\,A''q_{L''}\,J''$$

wherein each of J to J'' is a linking site or functionality as hereinbefore defined independently selected from a single or double bond, methylene, alkyne, alkene, NR, O, CONR, NRCO, S, CO, NCO, CHHal and P wherein R is H or C_{1-8} alkyl or cycloalkyl or forms part of a cyclic ring with N, Hal is any halogen selected from chlorine, iodine, bromine; and is present in any rational location in a group A to A'';
each of A to A '' is a group selected from –O-, -C(=O)-, C_{1-12} alkoxy, alkoyl, cycloalkyl, heterocyclic, alkyl, alkenyl, aryl, arylamide, arylamine, amino, thioalkyl, heteroaryl as hereinbefore defined and combinations thereof, optionally substituted by groups selected independently from C_{1-3} alkyl and C_{1-5} alkoxy;
each of q_L to $q_{L''}$ are independently-selected from 0 or 1 or indicates an oligomeric repeat and is from 2 to 30, or indicates a polymeric repeat unit and is from 31 up to 300.

$R_{L'}$ is a C, N or S atom or is a $CR_{L'}$, $NR_{L'}$, alkyl, cycloalkyl, heterocyclic, aryl heteroaryl, amine or thio moiety and provides for branching when p is 1 or 2; wherein $R_{L'}$ is H or C_{1-3} alkyl; and

p is as hereinbefore defined and is 0, 1 or 2.

8. Library as claimed in any of Claims 1 to 7 wherein J_{Lm} L J_{Tm} is of formula
J Aq_L R_L J''
wherein each of J and J'' is amine or –O-, A is CH_2CH_2O, q_L is 1-30 or 31 to 300 and R_L is CH_2CH_2
or of formula
J Aq_L R_L(A'J') J''
wherein each of J, J' and J'' independently is amine, –O or a single bond, q_L is 1, 2 or 3 -30 or 31 to 300 and A is CH_2CH_2O or $HNCH_2CO$ or q_L is 1 and A is C(O) or $(CH_2)_{1-8}$ or q_L is 0, R_L is CH or CH_2CH, $q_{L'}$ is 0 or q_L' is 1 and A' is CH_2 and $q_{L''}$ is 0
preferably
$O(CH_2CH_2O)q_LCH_2CH_2NH$, $O(CH_2CH_2O)q_LCH_2CH(CH_2NH)NH$,
$OCH(CH_2NH)NH$, $-CH(CH_2NH)NH$, -C(O) NH-, $-(CH_2)_{1-8}-$ or $(-HNCH_2CO-)_{1-3}$ (= -gly_{1-3}-) -.

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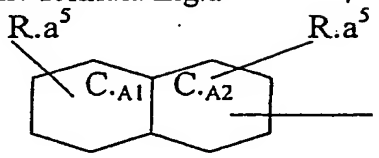
9. Library as claimed in any of Claims 1 to 8 wherein each compound of formula I or I' comprises a moiety Lig and L as hereinbelow defined:
Wherein:
any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers
$Lig.a_m$ is suitably of the formula, in either of the following forms given, including any of its possible linking configurations or sites:

$Lig.a^1{}_m$

Wherein at least one or all of Ra^1 to Ra^4, X^1 and X^2 comprise a linking site or functionality J as hereinbefore defined
X^1 and X^2 are each independently selected from H, O, OR.a, NR.a, NHR.a;
X^1 and X^2 are each preferably O;
each of $R.a^1$, $R.a^2$, $R.a^3$ and $R.a^4$ independently is selected from H or C_{1-4} linear or branched alkyl optionally mono or multi hydroxy or halo substituted;

$R.a^4$ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo and cyano; including optionally substituted aryl, cycloalkyl, alkyl, ketone, (di)amine, (di)amide, alkoxy, cycloalkyl, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein substituents include aryl, alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl or $R.a^4$ comprises cyclohexyl, cyclopentyl, ethoxy, $(CH_2)_2PhPh$, CH_2Ph, $CONH(CH_2)nCONH$, $CH_2CONH(CH_2)_2NH$, $CH_2PhNHCOCH_2$, $CH_2CH_2OCOCH_2$, succinimidyl ester, $NHCOCH_2$, $CH_2(CH_3)NCOCH_2$, $H_2N(CH_2)_2NHCOCH_2$, $H_2N(CH_2)_8NHCOCH_2$, $H_2NNHCOCH_2$, $CH_2CONH(CH_2)_2NHCOCH_2$, $HOPhCH_2N(CH_2CH_3.HOAc)(CH_2)_2NHCOCH_2$, heterocyclic-$(CH_2)_4CONH(CH_2)_2NHCOCH_2$ or heterocyclic-$NHCON$(heterocyclic)$COCH_2$;

or Lig.a is of the formula Lig.a^2-

Lig.a^2  R.a^6

wherein at least one or all of Ra^5 to Ra^6, or a cyclic C or heteroatom comprise a linking site or functionality J as hereinbefore defined, each of C.$_{A1}$ and C.$_{A2}$ is independently selected from C_{5-6} aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring –C=C- group;

Each of up to seven R.a^5 is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from H, halo, hydroxy, thiol, amine, COOH, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo =O or cyano; OCH_3, $CH_2Ph(OCH_3)_2$, $O(CH_2)_3CON(CH_3)$c.hex, $N(CH_2CH_2OH)_2$, c.hex, $COOCH_2CH_3$, CH_2CH_3;

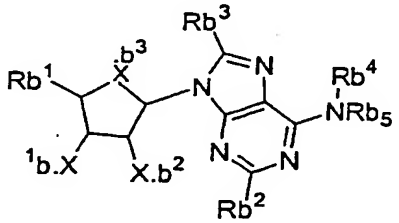
or any two or more of R.a^5 form a one, two or three ring fused cyclic structure, a fused 3 ring aryl, 5-heterocyclic or 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.a^{2}structure;

and R.a^6 is a moiety as defined for R.a^5 above;

and L.a is as hereinbefore defined for L or J_L L J_T or L.I or subformulae as hereinbefore defined, or is a single bond, amino acid or amide including a peptide or polypeptide gly or gly_3, alkyl of formula $-(CH_2)_n$ where n is 3 to 8, optionally including one or more heteroatoms or unsaturated groups, including –O- or –S- or –CH=CH-:

Lig.b is suitably of the formula Lig.b including any of its possible linking configurations or sites:

Lig.b



wherein at least one or all of Rb^1 to Rb^5 or Xb^1 to Xb^3 comprise a linking site or functionality J as hereinbefore defined

ring substituents X.b^1 and X.b^2 are independently selected from hydrocarbon including alkyl or SR_X, $NR_{X.2}$ and OR_X wherein (each) R_X is selected from H, C_{1-5}alkyl, alkenyl;

ring heteroatom X.b^3 is selected from –S-, -O- and $-CH_2$-;

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Rb^1 is selected from saturated or unsaturated, substituted or unsubstituted C_{1-4} aliphatic, or C_{1-3} alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine; or $R.b^1$ comprises a carbonyl substituted by H, alkyl or a linear or cyclic primary, secondary or tertiary amine, substituted C_{1-3} alkyl, cycloalkyl or amide, cyclopropyl, or $CONHC_{1-3}$alkyl including CONHEt or CH_2OH

and each of $R.b^2$ and $R.b^3$ is selected from H, halo, hydroxy, thiol, amine, COOH, CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano, preferably from H, halo or hydroxy;

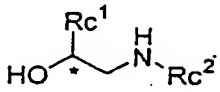
Rb^4 is H;

Rb^5 is H or alkyl

L.b comprises a linking site or functionality J as hereinbefore defined; and is as hereinbefore defined for L or its subformulae, more preferably is saturated and unsaturated substituted or unsubstituted C_{1-12} aliphatic or C_{1-24} aromatic as defined for L optionally including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, or is of formula L.I or its subformulae as hereinbefore defined, or is (CH_2)m wherein m is 2 to 12, or is $(Ph\text{-}CH_2CONH)_2$ $(CH_2)_2$;

Lig.c is of the formula Lig.c including any of its possible linking configurations or sites:

Lig.c $HOC^*(R.c^1)CH_2NH\text{-}R.c^2$



where at least one or all of Rc^1 to Rc^2 or OH, or a chain C or N comprise a linking site or functionality J as hereinbefore defined

* indicates an optically active centre and

wherein $R.c^1$ is C_{6-14} aryl optionally including one or more heteroatoms selected from H, O, optionally substituted by OH, Hal, NH_2, NHC_{1-3}alkyl, sulphonamide, oxoamine or (-$CONH_2$), or is mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH_2, or is m-CH_2OH, p-OH phenyl, m-,p-dihydroxy phenol or m-,m-dihydroxyphenol, m-,m-diCl, p-NH_2 phenol, p-OH, m-$CONH_2$ phenol or 5-OH, 8-quinoline,

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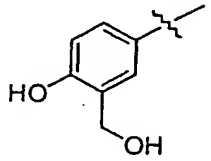
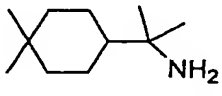
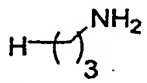


R.c^2 is selected from saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any optionally substituted C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano and combinations thereof; or R.c^2 is selected from C_{1-6} branched or straight chain aliphatic, C_{6-10} araliphatic optionally substituted by OH and optionally including heteroatoms selected from N,O, optionally including an ether O, and is selected from $-(CH_2)_6OCH((CH_2)_3Ph)$, $CHCH_3(CH_2)_2Ph$, $CHCH_3CH_2PhOH$, $C(CH_3)_2CH_2Ph$ or from the structures:

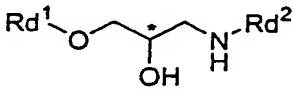




L.c is present as R.c^2 or comprises a linking site or functionality J as hereinbefore defined, and is as hereinbefore defined for L, formula L.I or its subformulae as hereinbefore defined, or is selected from C_{1-12} alkyl, amide;

Lig.d is of the formula Lig.d including any of its possible linking configurations or sites:

Lig.d R.d^1 $OCH_2C^*HOHCH_2NH$-R.d^2

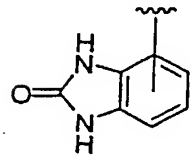
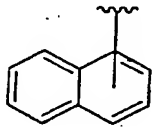
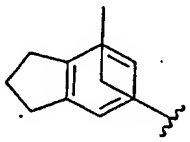
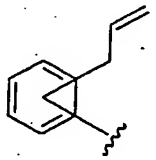
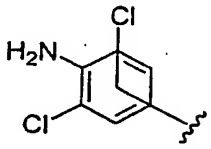


where at least one or all of Rd^1 to Rd^2 or OH, a chain C or N comprise a linking site or functionality J as hereinbefore defined

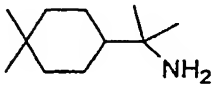
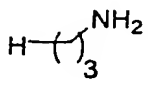
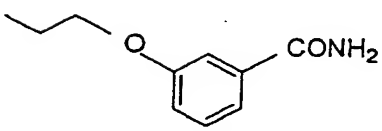
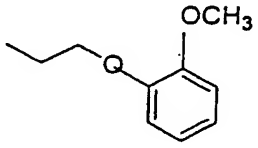
* indicates an optically active centre

wherein R.d^1 is saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano; or R.d^1 is substituted or unsubstituted C_{1-24} aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C_{1-6} alkyl, alkoxy, ether,

carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo or OH, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl including phenyl, carbazole or structures shown below or spiro ring systems, mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF_3 substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems:

R.d^2 is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C_{1-12} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano, more preferably amine, C_{1-6} branched or straight chain alkyl optionally including ether O, and optionally substituted by C_{6-10} aryl, or of the formula:

L.d may be present as R.d^2 or may comprise a linking site or functionality J as hereinbefore defined and is as hereinbefore defined for L and its

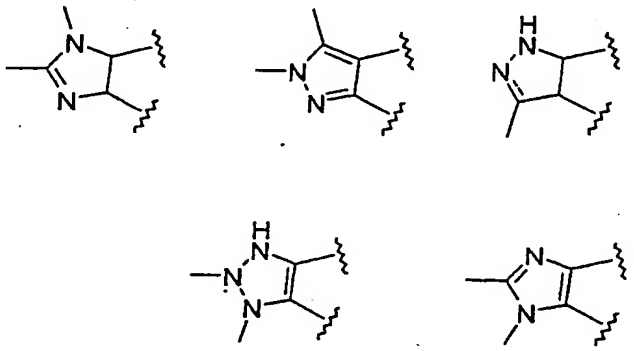
subformulae , formula L.I and its subformulae as hereinbefore defined, or is a single bond or is as hereinbefore defined for L.a;

Lig.e comprises a cell permeant moiety or is associated with a cell permeant L or Fl moiety or is of the formula , in either of the following forms given including any of its possible linking configurations or sites:

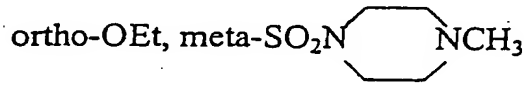
Lig.e[1]

wherein at least one or all of Re^1 to Re^4, X and a ring C or N comprise a linking site or functionality J as hereinbefore defined

h is selected from



each optionally substituted by $R.e^3$ – $R.e^4$ wherein $R.e^1$ – $R.e^4$ are as $R.a^1$ – $R.a^4$ defined above or in which $R.e^3$ is C_{5-9} linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy or sulfonyl,



each X is independently selected from H, O, -$OR.e^2$, N, HN, $NR.e^5$, $HR.e^6$, and aryl optionally substituted by ether; or X is aryl optionally alkyl or alkoxy substituted or is Ph-ortho-$OCH_2CH_2CH_3$;

and where $R.e^5$ is as defined above for $R.e^1$ above or forms a fused cyclic ring together with the adjacent ring N atom, or 1 or 2 fused 5 membered cyclic rings;

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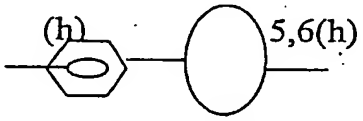
and $R.e^6$ is as defined above for $R.e^1$ above or is selected from optionally substituted phenyl wherein optional substituents include ether, o-ethoxy or o-propoxy, alkyl or OH, sulphonyl or carbonyl substituted by heterocyclic, or cyclic C_{5-8} alkyl, piperazinyl or sulphonyl;

or Lig.e is of the formula $Lig.e^2$

$Lig.e^2$ 

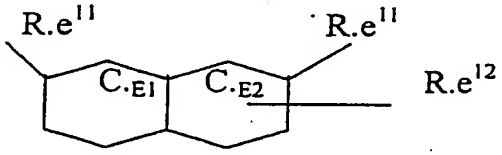
wherein at least one or all free ring atom or their substituents comprise a linking site or functionality J as hereinbefore defined

each spiro ring optionally comprises zero or one or more heteroatoms h

or  (h) comprises zero or 1 N heteroatom and  5,6(h) comprises zero, 1 or 2 N heteroatoms and is unsaturated or comprises one or two –C=C- or -C=N- groups;

and wherein each ring is optionally substituted by one or more oxo, CO, COOH, C_{1-6} alkyl or linear or cyclic alkoxy optionally substituted by one or more oxo, CO, COOH, CN, or C_{1-6} alicyclic or amine groups, amine or one or more spiro or fused heterocycles;

or Lig.e is of the formula $Lig.e^3$

$Lig.e^3$ 

wherein at least one or all of Re^{11} to Re^{12}, or a ring C or heteroatom or ring substituent comprise a linking site or functionality J as hereinbefore defined

each of $C._{E1}$ and $C._{E2}$ is independently selected from C_{5-6} aryl, heteroaryl, cyloalkyl and heterocyclic, including phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring –C=C- group;

each of up to seven $R.e^{11}$ is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may

comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo =O, or cyano, OCH_3, $CH_2Ph(OCH_3)_2$, $O(CH_2)_3CON(CH_3)$c.hex, $N(CH_2CH_2OH)_2$, c.hex, $COOCH_2CH_3$, CH_2CH_3;

or any two or more of R.e[11] form a one, two or three ring fused cyclic structure, a fused 3 ring aryl, 5-heterocyclic or 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.e[3] structure;

and R.e[12] is a moiety as defined for R.e[11] above;

L.e comprises a linking site or functionality J as hereinbefore defined and is suitably as hereinbefore defined for L.a.

10. Library as hereinbefore defined in any of Claims 1 to 9 wherein Fl is selected from dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein-like molecules including Oregon Green™ and its derivatives, Texas red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl chloride or its analogues or derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, erythosin, eosin, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including Rhodamine Green™ including the tetramethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol Green™, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.

11 Library as claimed in Claim 10 wherein Fl is of formula $J_T - t - Fl$ and comprises a BODIPY ™ structure characterised by a dipyrromethene boron difluoride core, optionally modified by one or two fused rings, optionally substituted by one or several substituents selected from alkyl, alkoxy, aryl or heterocyclic, wherein one substituent –t- is adapted for linking as hereinbefore defined to a ligand precursor as hereinbefore defined, wherein the substituent –t- comprises a proximal unsaturated or aryl moiety, comprising a medial short, medium or long chain alkynyl or cycloalkyl moiety and comprising a moiety derived from linking via a reactive group as hereinbefore defined or selected from carboxyl, sulphonate or as a heteroatom O or S or methylene derived from linking at an alkylhalide including methylbromide, haloacetamide or sulphonate ester electrophilic group.

12. Library as claimed in any of Claims 1 to 11 comprising a plurality of compounds of the formula

$Lig\ J_L\ L\ J_T\ Fl$

wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

wherein Fl is a fluorophore as hereinbefore defined in claim 10 or 11 and

wherein $Lig\ J_L\ L\ J_T$ is selected from:

xanthine like structures

adenosine like structures;

ethanolamine like structures; and

oxypropanolamine like structures; wherein

linking functionality J_T is amine; and
wherein linker L is selected from branched and straight chain C_{1-50} alkyl, C_{6-50} cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C_{1-12} aliphatic, or for xanthine like structures L is also selected from a single bond.

13. Process for the preparation of a library as claimed in any of Claims 1 to 12 which is a combinatorial process; and comprises the reaction of one or more ligand precursors of formula IV and/or IV'

IV $(LigJ_L)_m - L - Y_{Lm}$

IV' $Lig\ Y_{Ligm}$

comprising one or more or different reactive groups Y_L or Y_{Lig} forming a linking functionality J, J_L or J_T as hereinbefore defined
with one or more of a plurality of analytical tagging substrates of formula V and/or V'

V $Y_{Tm}\,Tag$

V' $Y_{Tm}\,L\,(J_T Tag)_m$

comprising one or more or different reactive groups Y_T forming a linking functionality J or J_T as hereinbefore defined
and optionally one or more linking species VI or VI' or VI''

VI $Y_{Lm}L\,Y_{Lm}$

wherein Lig, J, L, J_T and Tag and each m is independently as hereinbefore defined
wherein the or each compound of formula IV or IV' is capable of reaction with the or each compound of formula V or V', optionally via the or each species VI or VI' or VI'' to form a plurality of compounds of formula I as hereinbefore defined;
wherein linking is at same or different reactive sites in different compounds as hereinbefore defined.

14 Process for the preparation of a compound of formula I as hereinbefore defined in any of Claims 1 to 12 comprising the reaction of a compound of formula IV or IV' and a compound of formula V or V' and optionally additionally VI, as hereinbefore defined, by reacting the unprotected primary alkyl amine group of a compound of formula IV with a compound of formula V comprising a reactive succinimidyl ester group in solvent at ambient temperature without the need for subsequent deprotection.

15 Process for the preparation of a compound of formula IV as hereinbefore defined in Claim 13 or 14 comprising: obtaining where commercially available or preparing the ligand precursor Lig, by routes as known in the art, and reacting with linker precursor VI'', if required, or components thereof, and/or generating one or more reactive sites Y or Y_{Lig} or Y_L, by a method selected from:
a), e) ring closure of 5,6-diamino-1,3-dialkyl uracil with the appropriate substituted aldehyde under acid conditions with ferric chloride,
b) reacting Lig.b- comprising a protected inosine derivative with chlorinating agent and linking the chloro derivative with the amine group of a suitably protected amine reactive linker H–L-P_L wherein P_L comprises *N*-benzyloxycarbonyl- to form Lig.b -L-P_L and removing P_L to generate Lig.b –L.b; preferably R.b^1 comprises a OH terminating group and protected inosine comprises Acyl protecting groups or R.b^1 comprises a stable group such as amine or amide and protected inosine comprises 2,2-dimethoxypropane protecting group; preferably the protected inosine is reacted with

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oxidising agent and protected alkylamine which is an *N*-alkylcarboxamide with removal of amine protecting group to generate a reactive ligand;
c), d) reacting *p*-hydroxybenzaldehyde with formaldehyde under acid catalysis and protection of the resulting 4-hydroxy-3-hydroxymethylbenzaldehyde with dimethoxypropane to generate the resulting acetonide, converting the Benzaldehyde to its corresponding epoxide and ring opening with a suitably protected linker such as Boc-L.c-H supplies Lig_m-L-P_L, finally, deprotection under acid conditions supplies Lig.cLc or Lig.dLd for coupling to an appropriate tag.

16 Method for selecting a compound of formula I from a library as claimed in any of claims 1 to 12 comprising the rational design of a library of compounds of formula I as hereinbefore defined using the process as hereinbefore defined in Claim 13, determining pharmacology for a plurality of or all compounds in the library and selecting a compound exhibiting desired pharmacology.

17 Method as claimed in Claim 16 which comprises preparing a preliminary library of compounds, conducting screens to assess binding or inhibition, selecting a compound identified in the screen as having beneficial properties, and modifying or functionalising by nature of moieties or linking location of linking on the basis of the indications from the screen to prepare an optimised library, wherein the molecular pharmacology and photochemistry from the screen feedback into the design of the library.

18. A compound of formula I

$$(Lig\ J_L)_m\ L\ (J_T\ Tag)_m\ (J_T\ L\ (J_L\ Lig)_m)_p$$

or salt thereof as hereinbefore defined in Claim 1 or 2 or dependent claims wherein JL_m L T_{Tm} is as hereinbefore defined in Claim 8 and wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers.

19. A compound of formula II or III as hereinbefore defined in Claim 4 or dependent claims

II $(LigJ_L)_m$ L J_T TagJ_T L $(J_L\ Lig)_m$ where each m is as hereinbefore defined and is preferably 1 or 2, more preferably 1

III $(LigJ_L)_m$ L $(J_TTag)_m$ wherein each m is as hereinbefore defined and is preferably 1 and/or 2, more preferably

Lig J_L – L – J_L Tag and/or

Lig J_L – L – J_T Tag and/or Lig J_L – L – J_T Tag

J_L Lig J_T Tag

as hereinbefore defined in Claim 4 and wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers.

20. A compound according to Claim 18 or 19, wherein Lig or Fl is as hereinbefore defined in Claims 2, 6, 10 or 11.

21 A compound of the formula I or I' as hereinbefore defined in any of Claims 10 to 12 or 18 to 20 selected from formulae $Lig.a_m$ L.a-$Fl.a_n$ to $Lig.e_m$ L.e$Fl.e_n$ as hereinbefore defined
with the proviso that:

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a) when Lig is XAC ie in Lig.a when each of R.a^1 and R.a^2 is propyl, R.a^3 is H and R.a^4 is –Ph-$OCH_2CONH(CH_2)_2NH$-, and L is a single bond or L is gly and n=3 or L is NCS, Fl is not fluorescein; or

when Lig is XAC and L is a single bond or NCS, Fl is not fluorescein or NBD;

b) when Lig is adenosine Fl is not Fmoc (CA 134:204756); or

when Lig is ADAC , ie R.b^1 is CH_2OH, R.b^2 and R.b^3 are H and L is –(Ph-$CH_2CONH)_2(CH_2)_2$- or L is a single bond, Fl is not fluorescein, NBD or Rhodamine; or

when Lig is NECA (incorporating the moiety –(CH_2)m) ie R.b^2 and R.b^3 are H and L is a single bond, or is –(CH_2)m when m is 2,4,6,8 or 10 then Fl is not NBD, or when m is 3,4,6,8,10 or 12 then Fl is not dansyl; or

when Lig is N^6-[2-(4-aminophenyl)ethyl]adenosine and L is $(CH_2)_2PhNH$, Fl is not FITC (CA 131:56155 (8))

d) when Lig is CGP12177 and L (R.d^2) is mono amine menthane, Fl is not BODIPY® TMR; or

when Lig is CGP12177 and L is 1,1,4,4-tetramethyl butylamine, i.e $C(CH_3)_2(CH_2)_2C(CH_3)_2NH$- Fl is not BODIPY® FL, or when L is $C(CH_3)_2(CH_2)_2C(CH_3)_2NHCSNH$- then Fl is not FITC, eosin or erythosin; or when L is monoamine menthane, Fl is not FITC (CA 131:56155 (4)); or

when Lig is CGP12177 and L is a single bond, Fl is not NBD; or

when Lig is alprenolol i.e o-prop-2-enyl phenyl and L is –$C(CH_3)_2$- or a single bond, Fl is not NBD;

and a) – e) when L is a single bond, Fl is not BODIPY FL;

optionally additionally

a) when Lig is XAC ie in Lig.a when each of R.a^1 and R.a^2 is propyl, R.a^3 is H and R.a^4 is –Ph-$OCH_2CONH(CH_2)_2NH$-, and L is a single bond Fl is not BODIPY ™ 630/650 X; or

b) when Lig is ABEA, ie m is 4 and L is a single bond Fl is not BODIPY™ 630/650 X.

22. A compound of the formula

Lig J_L L J_T Fl as defined in any of claims 1 to 11 or 18 to 21
wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers
wherein Fl is a fluorophore as hereinbefore defined in claim 10 or 11 and
wherein Lig J_L L J_T is selected from:
xanthine like structures
adenosine like structures;
ethanolamine like structures; and
oxypropanolamine like structures; wherein
linking functionality J_T is amine; and
wherein linker L is selected from branched and straight chain C_{1-50} alkyl, C_{6-50} cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C_{1-12} aliphatic, or for xanthine like structures L is also selected from a single bond,
with the proviso that the compound is not a compound excluded in Claim 21.

23 A kit comprising a Compound of formula I or I' as hereinbefore defined in any of Claims 1 or 2 to 12, or 18 to 22 associated with information relating to its

pharmacological properties in the form of Spectral Properties given as Excitation Max and Emission Max, Fluorescence Lifetime and Emission quantum yield and Pharmacology defined in terms of cells expressing a GPCR receptor as hereinbefore defined or expressing an intracellular cyclic nucleotide phosphodiesterase, or a drug transporter as hereinbefore defined and given as the Inhibition or Antagonism of receptor binding or of receptor functionality together with a value for the Inhibition (pK_B) or Antagonism (pK_I) binding constants, and optionally together with fluorescent images of the pharmacological binding in single living cells illustrating the defined inhibition or antagonism, preferably the pharmacological properties are given as EC_{50} values for agonist stimulated – or pK_i values for antagonism of agonist stimulated second messenger generation, or substrate K_m values or antagonist K_i values for stimulation or inhibition of intracellular enzymes or drug transporters.

24 Compound of formula IV or IV' or library thereof as hereinbefore defined in Claim 13 useful for linking to any suitable tag of formula V or V' as hereinbefore defined in Claim 13,
wherein the linker moiety is of formula as defined in Claim 8.

25 Fluorophore linker of formula V' or library thereof as hereinbefore defined in any of Claims 13 to 14 wherein the linker moiety is of formula as defined in Claim 8..

26 Kit comprising ligand precursors, linker precursors and tag precursors of formulae IV, IV', V, V' and/or VI as hereinbefore defined in any of Claims 13 to 14 for preparing a library of compounds of formula I as hereinbefore defined in any of Claims 1 to 12.

27 A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof as hereinbefore defined in any of Claims 1 or 2 to 12, or 18 to 23 for visualising receptors or receptor binding, assessing pharmacological properties of the fluorescent ligand, in high throughput screening of novel chemical entities that bind to the target receptor, in inhibiting an intracellular enzyme or inhibiting a drug transporter or a substrate of a drug transporter, in studying drug transport or drugs suitable for transport or in distinguishing healthy or diseased tissue.

28 A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof thereof as hereinbefore defined in any of Claims 1 or 2 to 12, 18 to 23 for use in a method for receptor binding or inhibition, intracellular enzyme inhibition or drug transport or inhibition and visualisation comprising contacting a library or a compound thereof as defined in any of Claims 1 or 2 to 12 or 18 to 23 with a sample comprising live cell material comprising GPCRs, intracellular enzymes or drug transporters in manner to facilitate binding or inhibition thereof or transport thereby, and detecting changes in fluorescence or location thereof.

29. A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in Claim 28 wherein the library or compound thereof is a fluorescent ligand(s) which has affinity such that it binds permanently, semi-permanently or transiently and remains bound when unbound ligand is washed away.

30. A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in Claim 28 or 29 wherein detecting a change in

fluorescence is by means of confocal microscopy or fluorescence correlation spectroscopy.

31. A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in any of claims 28 to 30 wherein the library or compound thereof comprises fluorescent ligand agonist(s) which maintain binding affinity and functional activity.

32 A kit comprising a library or a compound of formula I or I' as claimed in any of Claims 1 or 2 to 12 or 18 to 23 and a target therefor provided as cell derived material selected from a cell line, expressing a GPCR, intracellular enzyme or drug transporter, membrane containing these proteins derived from such a cell line, solubilised receptor, enzyme or drug transporter or GPCR array from that cell line.

33 Kit as claimed in Claim 32 wherein the cell derived material is provided in one of three forms: (1) from cells expressing a green fluorescent protein tagged receptor, intracellular enzyme or drug transporter; (2) from cells expressing an epitope tag for a commercially available fluorescent antibody or (3) a wild-type protein for which a specific fluorescent antibody is also provided.

34. A library as hereinbefore defined in any of the preceding claims comprising a plurality of defined and characterised ligands having verified properties corresponding to those of the non-tagged ligand.

35. A library as hereinbefore defined in any of the preceding claims comprising tagged ligands designed from reaction of reactive precursor ligands and reactive fluorophores having reactive site chemical functionality suited for reaction with associated reagents, for site specific reaction and linking, wherein the library design is the result of extensive pharmacological investigation of all or many of the possible linking sites and the resulting pharmacological characteristics and selection of one or more linking combinations which provide favorable binding, inhibition or transport characteristics.

36. A library or compound as hereinbefore defined in any of the preceding claims wherein the or each Fl is selected from any red, near ir or blue absorbing dye or from BODIPY® 630/650 or BODIPY® 630/650 X.

37. Library as claimed in Claim 12 comprising a plurality of compounds of the formula

Lig J_L L J_T Fl

wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

wherein Fl is selected from any fluorophore as defined in Claim 10 or 11 and

wherein Lig J_L L J_T is selected from the formulae Lig.a, Lig.b, Lig.c and Lig.d wherein:

Lig.a comprises linking functionality J_L which is amine, and is of the formula, in either of the following forms given:

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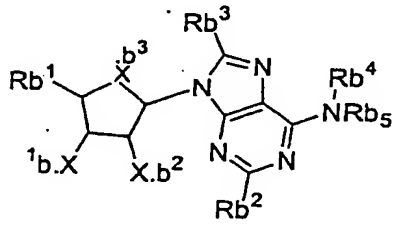
Lig.a $^{1}_{m}$

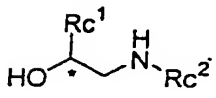
wherein Ra^4 comprises linking functionality J_L and J_T which is amine;
X^1 and X^2 are each O;
$R.a^3$ is H;
each of $R.a^1$ and $R.a^2$ is n-propyl;
$R.a^4$ is p- substituted phenyl wherein the substituent is heteroalkyl amide amine; and includes L which is a single bond or is C_{1-50} alkyl optionally substituted by C_1 alkyl and including the formula $-(CH_2)_n$ where n is 3 to 8, optionally including one or more heteroatoms –O;

Lig.b comprises linking functionality J_L which is amine, and is



wherein ring substituents $X.b^1$ and $X.b^2$ are each OH;
ring heteroatom $X.b^3$ is -O- ;
Rb^1 is CONHEt or CH_2OH;
and each of $R.b^2$ and $R.b^3$ is H;
Rb^4 is H;
Rb^5 comprises linking functionality J_T which is amino, and linker L.b selected from saturated C_{1-12} aliphatic and C_{6-24} aromatic, optionally substituted by one or more C_1 alkyl and optionally including one or more heteroatoms O or cyclic groups;

Lig.c comprises linking functionality J_L which is amine and is



as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,
Rc^1 is m-, p- dihydroxyphenyl; and

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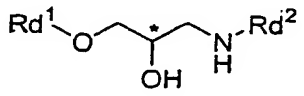
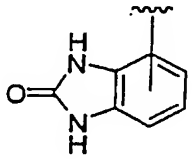
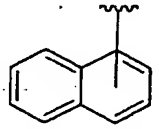
Rc^2 comprises linking functionality J_T which is amine, and linker L.c which is selected from C_{1-12} straight chain alkyl, C_{6-12} cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C_1 aliphatic;

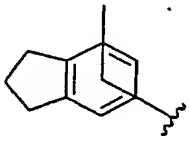
or Lig.d comprises a linking functionality J_L which is amine and is

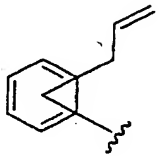


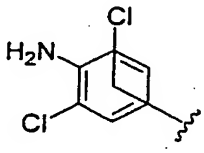
as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,
Rd^1 is selected from the structures







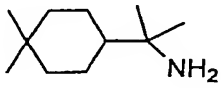


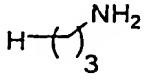


and a substituted C_{1-20} spiro aromatic ring system comprising a single aromatic ring and a heteroaryl and optionally halo substituted; and

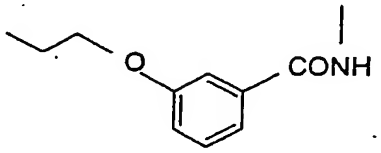
Rd^2 comprises linking functionality J_T which is amine, and linker L.d which is selected from C_{1-12} straight chain alkyl, C_{6-12} cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C_1 aliphatic; or Rd^2 is C_{1-6} straight chain alkyl including ether O and substituted by C_{6-10} aryl which is OH and oxo substituted and comprises linker L.d as hereinbefore defined.

38. Library as claimed in claim 37 wherein
$R.a^4$, $R.b^5$ or $R.c^2$ or $R.d^2$ comprises linking functionality J_T which is amino, and linker L.a, L.b, L.c or L.d selected from $(CH_2)m$ wherein m is 3, 4, 6 or 8 or is in the range 3 to 8 or 2 to 12 optionally including one or more substituents C_1, or J_L L J_T is mono or polyethylene glycol diamine, or L.a is a single bond; or
$R.c^2$ or $R.d^2$ comprises linking functionality J_T which is amino, and linker L.c or L.d selected from $C(CH_3)_2CH_2Ph$ and mono amino menthane or the structure





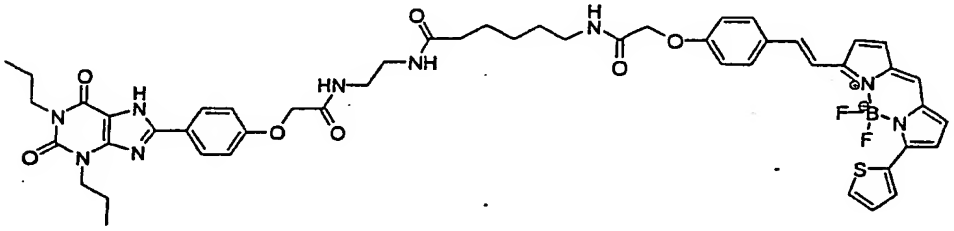
or Rd^2 comprises the following OH substituted aryl structure wherein linking functionality J_L is shown as amine, Ld is as hereinabove defined and includes J_T which is amine:



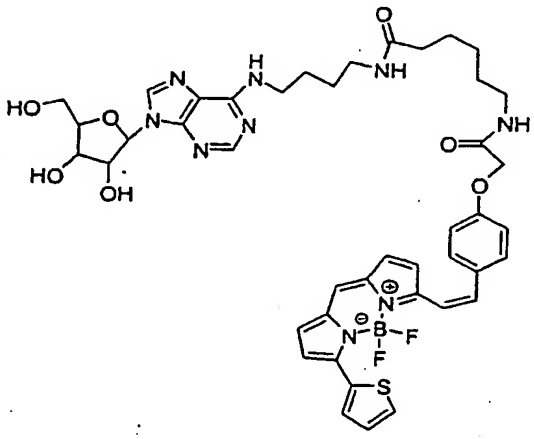
39. Library as claimed in Claim 37 or 38 wherein Fl is selected from any red, near ir or blue dye.

40. Library as claimed in Claim 37 or 38 wherein Fl is selected from BODIPY 630/650 X and BODIPY 630/650.

41. Library as claimed in any of the preceding Claims comprising a compound selected from the following structures wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers:



XAC – BODIPY 630/650 X



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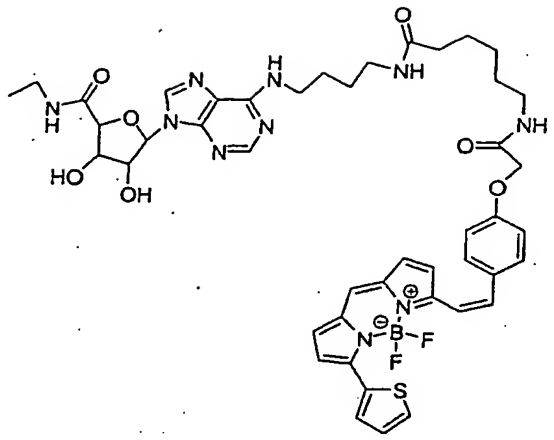
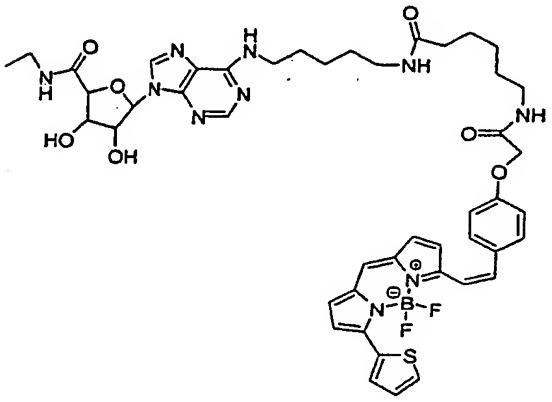
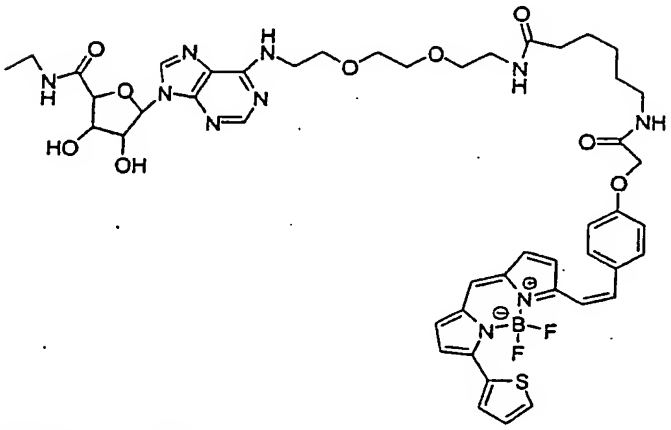


ABEA-BY630

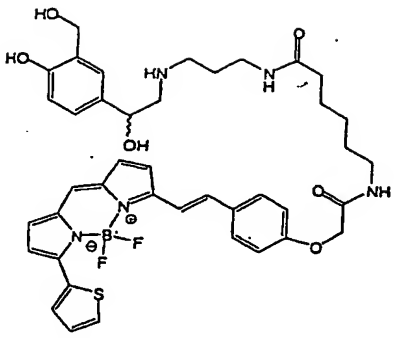


APEA-BY 630

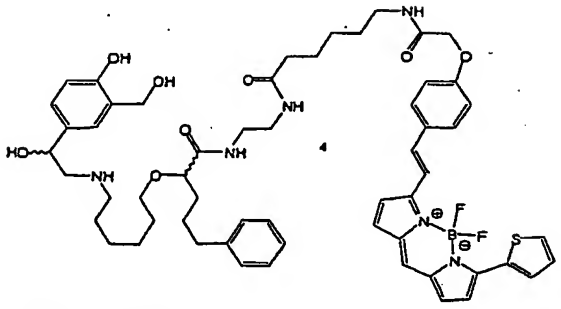


ABIPEA – BY630

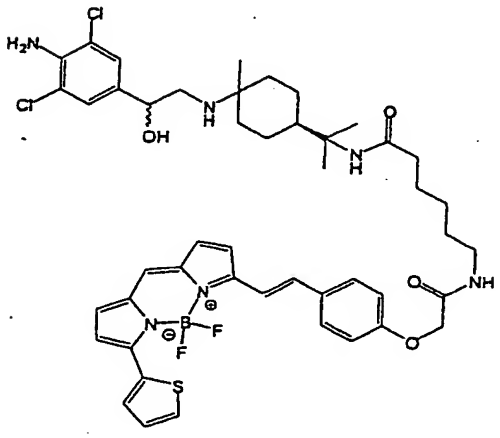
AMENDED SHEET



and



Salmeterol BY 630/650



Clenbuterol BY 630/650

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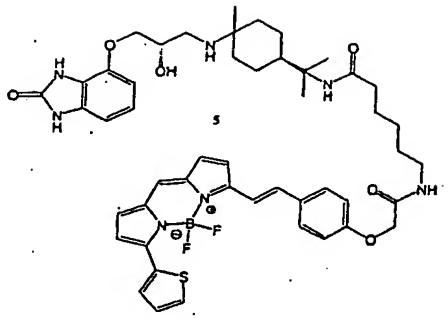
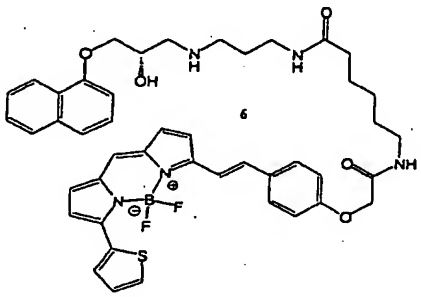
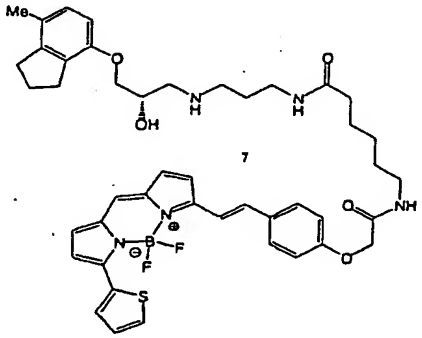


CGP12177-BY 630/650



Propranolol BY630/650



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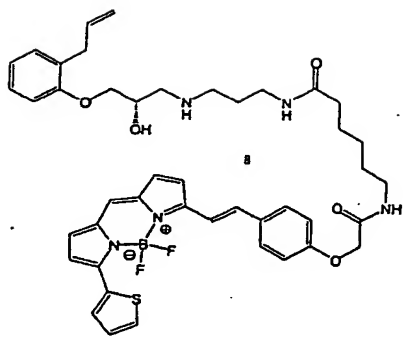

Alprenolol-BY630/650

42. Compound as claimed in Claim 21 of the formula

Lig J_L L J_T Fl
wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers
wherein Fl is selected from any fluorophore as defined in Claim 10 or 11 and
wherein Lig J_L L J_T is selected from the formulae Lig.a, Lig.b, Lig.c and Lig.d wherein:

Lig.a comprises linking functionality J_L which is amine, and is of the formula, in either of the following forms given:

Lig.a $^{1}_{m}$

wherein Ra^4 comprises linking functionality J_L and J_T which is amine;
X^1 and X^2 are each O;
$R.a^3$ is H;
each of $R.a^1$ and $R.a^2$ is n-propyl;
$R.a^4$ is p- substituted phenyl wherein the substituent is heteroalkyl amide amine; and includes L which is a single bond or is C_{1-50} alkyl optionally substituted by C_1 alkyl and including the formula $-(CH_2)_n$ where n is 3 to 8, optionally including one or more heteroatoms –O;

Lig.b comprises linking functionality J_L which is amine, and is

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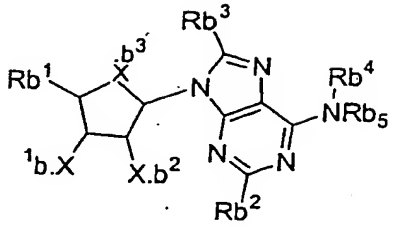
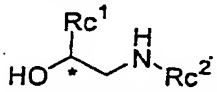


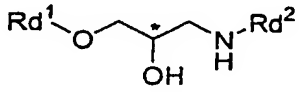
wherein ring substituents $X.b^1$ and $X.b^2$ are each OH;
ring heteroatom $X.b^3$ is -O- ;
Rb^1 is CONHEt or CH_2OH;
and each of $R.b^2$ and $R.b^3$ is H;
Rb^4 is H;
Rb^5 comprises linking functionality J_T which is amino, and linker L.b selected from saturated C_{1-12} aliphatic and C_{6-24} aromatic, optionally substituted by one or more C_1 alkyl and optionally including one or more heteroatoms O or cyclic groups;

Lig.c comprises linking functionality J_L which is amine and is

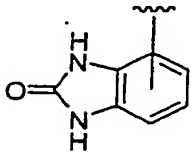


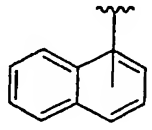
as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,
Rc^1 is m-, p- dihydroxyphenyl; and
Rc^2 comprises linking functionality J_T which is amine, and linker L.c which is selected from C_{1-12} straight chain alkyl, C_{6-12} cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C_1 aliphatic;

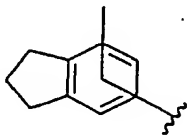
or Lig.d comprises a linking functionality J_L which is amine and is

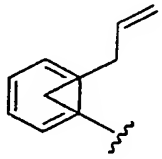


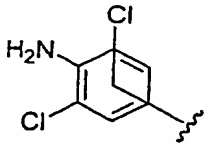
as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,
Rd^1 is selected from the structures











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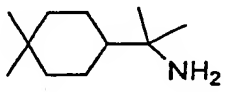
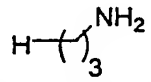
and a substituted C_{1-20} spiro aromatic ring system comprising a single aromatic ring and a heteroaryl and optionally halo substituted; and

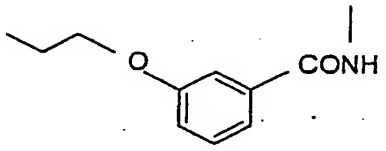
Rd^2 comprises linking functionality J_T which is amine, and linker L.d which is selected from C_{1-12} straight chain alkyl, C_{6-12} cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C_1 aliphatic; or Rd^2 is C_{1-6} straight chain alkyl including ether O and substituted by C_{6-10} aryl which is OH and oxo substituted and comprises linker L.d as hereinbefore defined,
with the proviso that the compound is not a compound excluded in Claim 18.

43. Compound as claimed in Claim 42 wherein $R.a^4$, $R.b^5$ or $R.c^2$ or $R.d^2$ comprises linking functionality J_T which is amino, and linker L.a, L.b, L.c or L.d selected from $(CH_2)m$ wherein m is 3, 4, 6 or 8 or is in the range 3 to 8 or 2 to 12 optionally including one or more substituents C_1, or J_L L J_T is mono or polyethylene glycol diamine, or L.a is a single bond; or
$R.c^2$ or $R.d^2$ comprises linking functionality J_T which is amino, and linker L.c or L.d selected from $C(CH_3)_2CH_2Ph$ and mono amino menthane or the structure





or Rd^2 comprises the following OH substituted aryl structure wherein linking functionality J_L is shown as amine, Ld is as hereinabove defined and includes J_T which is amine:



with the proviso that the compound is not a compound excluded in Claim 21.

44. Compound as claimed in Claim 42 or 43 wherein Fl is selected from any red, near ir or blue dye.

45. Compound as claimed in Claim 42 or 43 wherein Fl is selected from BODIPY 630/650 X and BODIPY 630/650.

46. Compound selected from the structures wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers:

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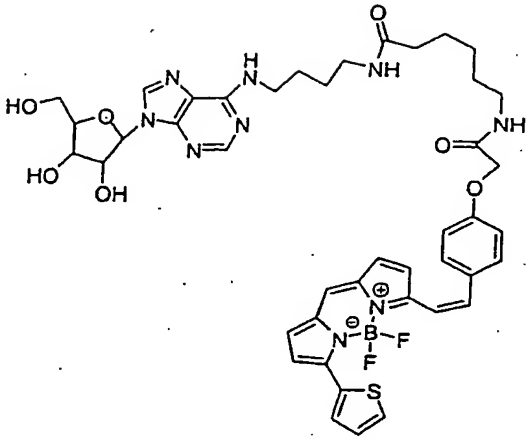
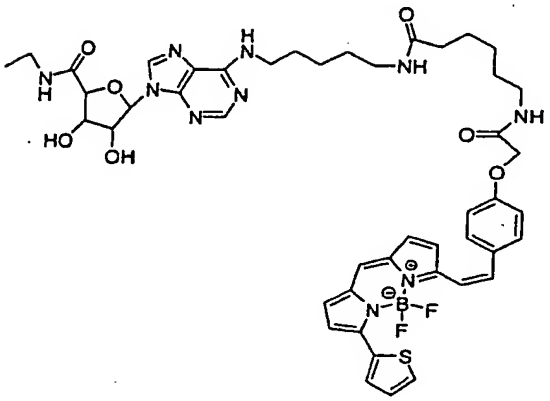
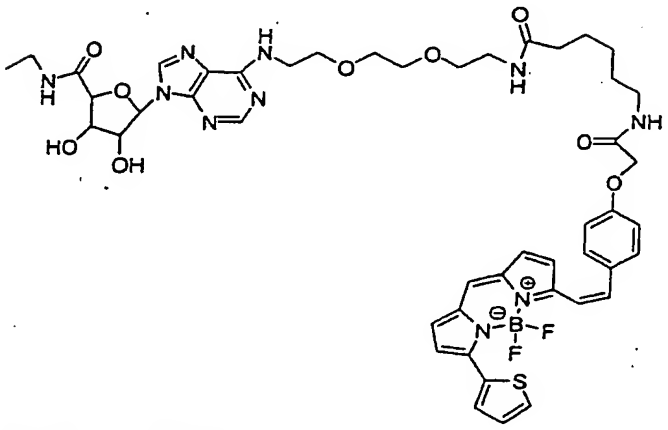


ABA-BY630



APEA-BY 630



ABIPEA – BY630

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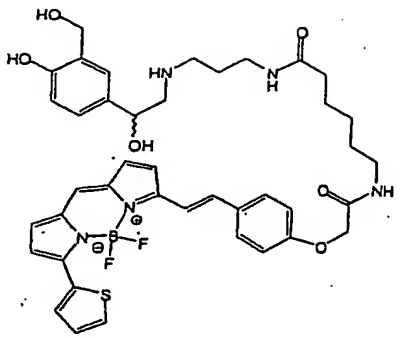
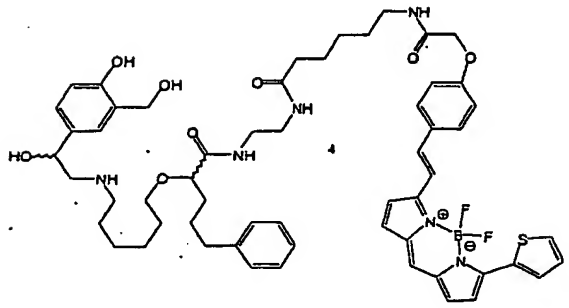
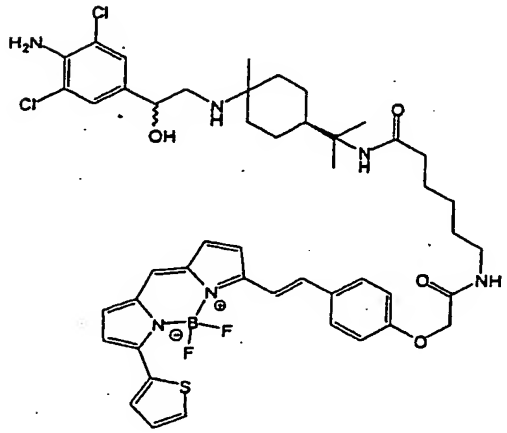


and



Salmeterol BY 630/650



Clenbuterol BY 630/650

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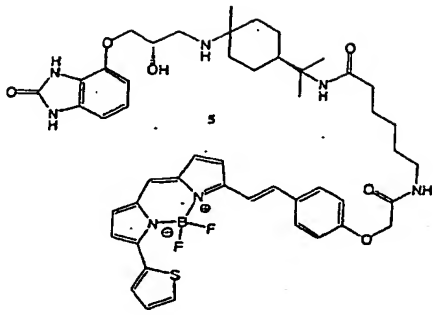
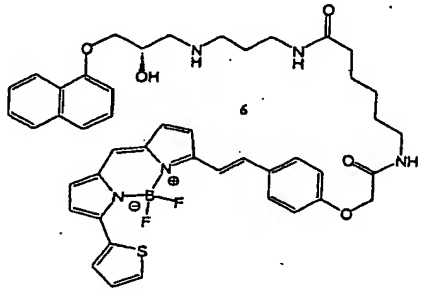
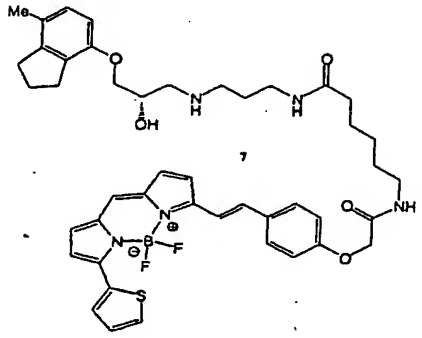


CGP12177-BY 630/650



Propranolol BY630/650



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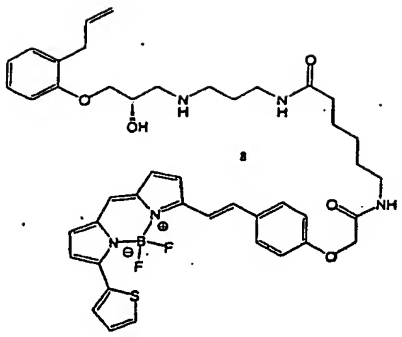
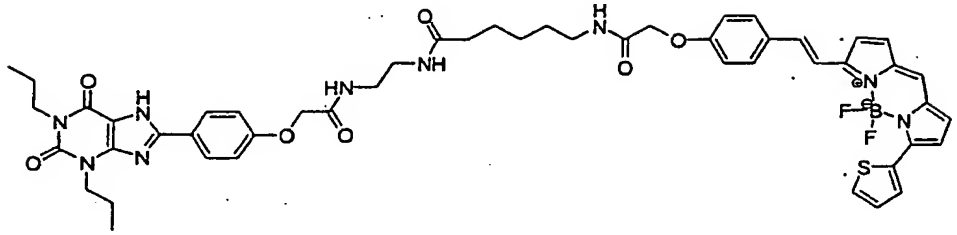


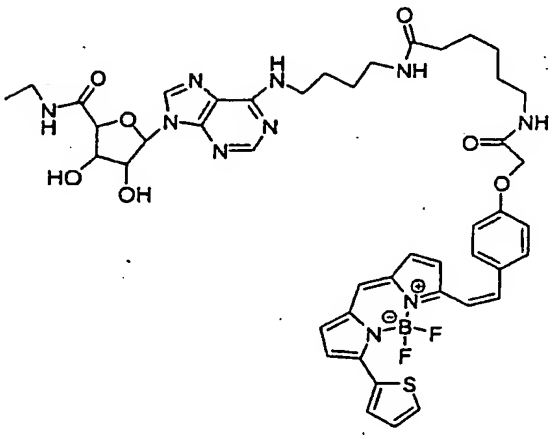
Alprenolol-BY630/650

and optionally additionally



XAC – BODIPY 630/650 X

or



ABEA-BY630.

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